office

L2 ANSWER 65 OF 69 CAPLUS COPYRIGHT 2002 ACS
AN 1995:563071 CAPLUS
DN 123:25428
TI S-alkyl-**L-thiocitrullines**. Potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo
AU Narayanan, Krishnaswamy; Spack, Larry; McMillan, Kirk; Kilbourn, Robert G.; Hayward, Michael A.; Masters, Bettie Sue Siler; Griffith, Owen W.
CS Departments of Biochemistry and Pediatrics, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SO J. Biol. Chem. (1995), 270(19), 11103-10
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Nitric oxide synthase catalyzes the oxidn. of a guanidino nitrogen of L-arginine to nitric oxide with concomitant formation of citrulline. Enzyme activity is inhibited by a variety of N.omega.-monosubstituted L-arginine analogs including N.omega.-alkyl-, N.omega.-amino-, and N.omega.-nitro-L-arginine derivs. The authors report here that both constitutive and inducible isoforms of nitric oxide synthase are strongly inhibited by S-alkyl-**L-thiocitrullines** (N.delta.-(S-alkyl)isothioureido-L-ornithines) with n-alkyl groups of one to three carbons. These compds. represent a novel class of inhibitors and are the most potent nitric oxide synthase-inhibiting amino acids described to date. Inhibition is reversible, stereoselective, and competitive with L-arginine. Spectral studies show no direct interaction of inhibitor sulfur with heme iron, a result in contrast to that seen previously with the parent compd., **L-thiocitrulline**. The S-alkyl-**L-thiocitrullines** have strong pressor activity in normotensive control rats; S-methyl-**L-thiocitrulline** reverses hypotension in a rat model of septic peritonitis and in dogs administered endotoxin. These latter findings suggest that the inhibitors may have therapeutic utility in treating hypotension due to the overprodn. of nitric oxide.
ST alkylthiocitrulline nitric oxide synthase inhibitor antihypotensive
IT Antihypotensives
Kinetics, enzymic
(alkylthiocitrullines as potent stereoselective inhibitors of nitric oxide synthase with strong pressor activity in vivo)
IT Molecular structure-biological activity relationship

(nitric oxide synthase-inhibiting; alkylthiocitrullines as potent
stereoselective inhibitors of nitric oxide synthase with strong pressor
activity in vivo)
IT 158875-72-0P, S-Ethyl-**L-thiocitrulline** 160203-44-1P
164228-82-4P 164228-83-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic
preparation); THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); USES (Uses)
(alkylthiocitrullines as potent stereoselective inhibitors of nitric
oxide synthase with strong pressor activity in vivo)
IT 156719-39-0 164228-81-3
RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylthiocitrullines as potent stereoselective inhibitors of nitric
oxide synthase with strong pressor activity in vivo)
IT 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(alkylthiocitrullines as potent stereoselective inhibitors of nitric
oxide synthase with strong pressor activity in vivo)

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OFFice

L1 ANSWER 68 OF 70 CAPLUS COPYRIGHT 2002 ACS
AN 1996:7152 CAPLUS
DN 124:106558
TI **L-N6-(1-Iminoethyl)-lysine** potently inhibits inducible nitric oxide synthase and is superior to NG-monomethyl-arginine in vitro and in vivo
AU Stenger, Steffen; Thuering, Heike; Roellinghoff, Martin; Manning, Pamela; Bogdan, Christian
CS Institute of Clinical Microbiology and Immunology, University of Erlangen, Erlangen, Germany
SO Eur. J. Pharmacol. (1995), 294(2/3), 703-12
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 13
AB **L-N6-(1-Iminoethyl)-lysine** is a novel inhibitor of nitric oxide (NO) synthase, which similar to aminoguanidine but unlike NG-monomethyl-L-arginine is 30-fold more selective for the inducible than for the constitutive isoform of the enzyme. Here, the authors characterized this inhibitor for the first time in intact cells and during infection of mice with a NO-sensitive parasite (Leishmania major). **L-N6-(1-Iminoethyl)-lysine** potently inhibited the activity of inducible NO-synthase in primary macrophages. After stimulation by interferon-.gamma., the IC50 of **L-N6-(1-iminoethyl)-lysine** was 0.4 .mu.M and 10- or 30-fold lower than that of NG-monomethyl-L-arginine or aminoguanidine, resp. In vivo, **L-N6-(1-iminoethyl)-lysine** (0.4-9 mM in the drinking water) suppressed inducible NO-synthase activity and caused a dramatic exacerbation of leishmaniasis, despite a counterregulatory increase of inducible NO-synthase protein in the tissue. In contrast, considerably higher concns. of NG-monomethyl-L-arginine (20-50 mM) were required to achieve comparable effects. NG-Monomethyl-L-arginine, but not **L-N6-(1-iminoethyl)-lysine** led to wt. loss, reduced water and food consumption. The authors conclude that **L-N6-(1-iminoethyl)-lysine** should be used instead of NG-monomethyl-L-arginine for potent suppression of inducible NO-synthase in vitro and in vivo.
ST iminoethyllysine inducible nitric oxide synthase inhibitor; methylarginine inducible nitric oxide synthase inhibitor; lysine deriv nitric oxide synthase inhibitor
IT Leishmania major
(infection with; (iminoethyl)lysine potently inhibits inducible nitric

office

1: Photochem Photobiol 2002 Sep;76(3):335-40 Related Articles, Links

Wavelength-dependent properties of photodynamic therapy using hypericin in vitro and in an animal model.

Blank M, Kostenich G, Lavie G, Kimel S, Keisari Y, Orenstein A.

Department of Human Microbiology, Sackler School of Medicine, Tel Aviv University, Israel.

Wavelength effects in photodynamic therapy (PDT) with hypericin (HY) were examined in a C26 colon carcinoma model both in vitro and in vivo. Irradiation of HY-sensitized cells in vitro with either 550 or 590 nm caused the loss of cell viability in a drug- and light-dose-dependent manner. The calculated ratio of HY-based PDT (HY-PDT) efficiencies at these two wavelengths was found to correlate with the numerical ratio of absorbed photons at each wavelength. In vivo irradiation of C26-derived tumors, 6 h after intraperitoneal administration of HY (5 mg/kg), caused extensive vascular damage and tumor necrosis. The depth of tumor necrosis (d) was more pronounced at 590 than at 550 nm and increased when the light dose was raised from 60 to 120 J/cm2. The maximal depths of tumor necrosis (at 120 J/cm2) were 7.5+/-1.5 mm at 550 nm and 9.9+/-0.8 mm at 590 nm. Both values are rather high in view of the limited penetration of green-yellow light into the tissue. Moreover, the depth ratio, d590/d550 = 1.3 ($P < 0.001$), is smaller than expected considering the 2.2-fold lower HY absorbance and the 1.7-fold lower tissue penetration of radiation at 550 than at 590 nm. This finding indicates that in vivo the depth at which HY-PDT elicits tumor necrosis is not only determined by photophysical considerations (light penetration, number of absorbed photons) but is also influenced significantly by other mechanisms such as vascular effects. Therefore, despite the relatively short-wavelength peaks of absorption, our observations suggest that HY is an effective photodynamic agent that can be useful in the treatment of

tumors with depths in the range of 1 cm.

PMID: 12403456 [PubMed - in process]

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d his

(FILE 'HOME' ENTERED AT 15:35:18 ON 21 NOV 2002)

FILE 'CAPLUS' ENTERED AT 15:35:50 ON 21 NOV 2002

L1 41 S N-ACETYLCOLCHINOL
L2 3 S L1 AND VASCULAR
L3 3 DUP REM L2 (0 DUPLICATES REMOVED)

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L3   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2002 ACS
AN   2002:51447  CAPLUS
DN   136:102557
TI   Preparation of colchinol derivatives as vascular damaging agents
IN   Arnould, Jean Claude; Lamorlette, Maryannick Andree
PA   Angiogene Pharmaceuticals Limited, UK
SO   PCT Int. Appl., 82 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
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PI   WO 2002004434      A1    20020117       WO 2001-GB2966   20010704
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
             UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 2001066233      A5    20020121       AU 2001-66233    20010704
PRAI EP 2000-401978     A     20000707
     WO 2001-GB2966     W     20010704
OS   MARPAT 136:102557
RE.CNT  4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT


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L3   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2002 ACS
AN   2001:747617  CAPLUS
DN   135:283180
TI   Combination therapies using ZD6126 with a platinum antitumor agent, a
     taxane, or ionizing radiation for vascular damaging activity
IN   Davis, Peter David; Dougherty, Graeme
PA   Angiogene Pharmaceuticals Ltd., UK
SO   PCT Int. Appl., 47 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
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PI   WO 2001074368      A1    20011011       WO 2001-GB1317   20010327
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
             RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI GB 2000-7740       A     20000331
     GB 2000-13927      A     20000608
     GB 2000-14908      A     20000620
RE.CNT  5      THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT
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=> d l3 3

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 2000:475616 CAPLUS
DN 133:89673
TI Preparation of colchinol derivatives for use as **vascular** damaging agents
IN Davis, Peter David; Arnould, Jean-Claude; Boyle, Francis Thomas
PA Angiogene Pharmaceuticals Ltd., UK
SO PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040529	A1	20000713	WO 1999-GB4436	19991224
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1140745	A1	20011010	EP 1999-962468	19991224
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 9916790	A	20011204	BR 1999-16790	19991224
	JP 2002534400	T2	20021015	JP 2000-592241	19991224
	NO 2001003367	A	20010905	NO 2001-3367	20010706
PRAI	GB 1999-334	A	19990107		
	WO 1999-GB4436	W	19991224		

OS MARPAT 133:89673
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

Your SELECT statement is:
s vascular(w)damage

Items	File
1799	5: Biosis Previews(R)_1969-2002/Nov W3
1181	34: SciSearch(R) Cited Ref Sci_1990-2002/Nov W4
39	35: Dissertation Abs Online_1861-2002/Oct
6	48: SPORTDiscus_1962-2002/Nov
26	65: Inside Conferences_1993-2002/Nov W3
377	71: ELSEVIER BIOBASE_1994-2002/Nov W3
1580	73: EMBASE_1974-2002/Nov W3
11	91: MANTIS(TM)_1880-2002/Oct
217	94: JICST-EPlus_1985-2002/Sep W3
36	98: General Sci Abs/Full-Text_1984-2002/Oct
17	135: NewsRx Weekly Reports_1995-2002/Nov W2
480	144: Pascal_1973-2002/Nov W3
278	149: TGG Health&Wellness DB(SM)_1976-2002/Nov W2
1593	155: MEDLINE(R)_1966-2002/Nov W3
341	156: ToxFile_1965-2002/Nov W3
337	159: Cancerlit_1975-2002/Oct
41	162: CAB Health_1983-2002/Oct
3	164: Allied & Complementary Medicine_1984-2002/Nov
22	172: EMBASE Alert_2002/Nov W3
55	266: FEDRIP_2002/Sep
1	369: New Scientist_1994-2002/Oct W3
3	370: Science_1996-1999/Jul W3
144	399: CA SEARCH(R)_1967-2002/UD=13721
168	434: SciSearch(R) Cited Ref Sci_1974-1989/Dec
148	442: AMA Journals_1982-2002/Dec B2
49	444: New England Journal of Med._1985-2002/Nov W4
2	467: ExtraMED(tm)_2000/Dec

SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2002/Nov W3
(c) 2002 BIOSIS
***File 5: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Nov W3
***File 155: For updating information please see Help News155. Alert** feature enhanced with customized scheduling. See HELP ALERT.

1/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13962978 BIOSIS NO.: 200200591799
Uptake of the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and activation of NF-kappaB in human tumor cell lines.
AUTHOR: Woon See-Tarn(a); Baguley Bruce C; Palmer Brian D; Fraser John D; Ching Lai-Ming
AUTHOR ADDRESS: (a)Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, Private Bag 92019, Auckland**New Zealand
E-Mail: st.woon@auckland.ac.nz
JOURNAL: Oncology Research 13 (2):p95-101 2002
MEDIUM: print
ISSN: 0965-0407
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 5,6-Dimethylxanthenone-4-acetic acid (DMXAA), a new anticancer drug synthesized in this laboratory and currently in clinical trial, induces tumor **vascular damage** in vivo that is mediated primarily by cytokine synthesis by host cells. Although its pharmacology and antitumor activity have been extensively studied, little is known of its action on tumor cell lines. We measured (3H)DMXAA uptake in the Raji, Daudi, Jurkat, ECV304, N2M12, HL60, and K562 human tumor lines using velocity centrifugation through silicon oil layers, and also measured NF-kappaB activation by electrophoretic mobility shift assays. All lines accumulated (3H)DMXAA, and uptake by ECV304 cells was rapid, pH dependent

(greater uptake at pH 6.5), similar at 4degreeC and 37degreeC, and unaffected by the addition of 5 mM sodium azide. The uptake ratio was 4.5-fold at a low drug concentration (4 muM) and decreased significantly (P<0.01) to 4.0 as the external drug concentration was increased to 0.7 mM, providing evidence of saturability. (3H)DMXAA interacted weakly with isolated cytoplasmic proteins, as measured by equilibrium dialysis, providing a basis for the observed cellular uptake. Uptake was slightly reduced by addition of a less potent analogue, flavone acetic acid, or of an inactive analogue, 8-methylxanthenone-4-acetic acid, suggesting competition for binding sites. The Raji, Daudi, Jurkat, and ECV304 lines showed evidence of activation of the NF-kappaB transcription factor in response to DMXAA, but the identity of the NF-kappaB subunits translocated to the nucleus varied according to the line. The results are consistent with the hypothesis that DMXAA is taken up rapidly into cells by passive diffusion and binds to cellular proteins. The observed activation of NF-kappaB in some lines suggests that the effects of DMXAA on tumor cells, as well as host cells, must be considered in understanding its antitumor action.

REGISTRY NUMBERS: 117570-53-3: 5 6-DIMETHYLXANTHENONE-4-ACETIC ACID; 117570-76-0: 8-METHYLXANTHENONE-4-ACETIC ACID; 87626-55-9: FLAVONE ACETIC ACID; 26628-22-8: SODIUM AZIDE

1/9/9 (Item 9 from file: 5)

13953755 BIOSIS NO.: 200200582576

[New aspects of antineutrophil cytoplasmic antibodies (ANCA) in vasculitides.]

ORIGINAL LANGUAGE TITLE: Neue Aspekte der Antineutrophile zytoplasmatische Antikoerper (ANCA)-Diagnostik bei Vaskulitiden.

AUTHOR: Csernok E(a); Reichel P; Gross W L
AUTHOR ADDRESS: (a)Rheumaklinik Bad Bramstedt, Oskar-Alexander-Str. 26, 24572, Bad Bramstedt**Germany E-Mail: Csernok@rheuma-zentrum.de

JOURNAL: Zeitschrift fuer Rheumatologie 61 (4):p367-377 August, 2002
MEDIUM: print
ISSN: 0340-1855
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English

ABSTRACT: Anti-Neutrophil Cytoplasmic Antibodies (ANCA) are a heterogenous group of autoantibodies with a broad spectrum of clinically associated diseases. The diagnostic value is established of Proteinase 3 (PR3)-ANCA for Wegener's granulomatosis (WG) as well as Myeloperoxidase (MPO)-ANCA for microscopic polyangiitis (MPA). Within the last 20 years these antibodies were subject of intensive studies and a growing body of evidence arose for a distinct role of ANCA in the pathogenesis of the ANCA associated vasculitides WG and MPA. Our current concept of whether ANCA directly or indirectly contribute to **vascular damage** (ANCA-Cytokine-Sequence-Theory) was mainly developed from in vitro studies. It is plausible and it is supported by data from clinical investigations as well as animal models. Nevertheless our knowledge of the etiological and pathogenetic pathways remains incomplete.

1/9/13 (Item 13 from file: 5)

13945230 BIOSIS NO.: 200200574051

Gangrene of the toes in a patient with chronic myelogenous leukemia after long-term hydroxyurea therapy.

AUTHOR: Leo E(a); Kraemer A; Hochhaus A; Krasniqi F; Hehlmann R; Ho A D
AUTHOR ADDRESS: (a)Abteilung fuer Haematologie, Onkologie und Rheumatologie, Universitaetsklinikum Heidelberg, Hospitalstr. 3, 69115, Heidelberg**Germany E-Mail: Eugen.Leo@med.uni-heidelberg.de

JOURNAL: Annals of Hematology 81 (8):p467-469 August, 2002
MEDIUM: print
ISSN: 0939-5555
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Gangrene of the toes and digits appears to be a rare but very severe complication of long-term hydroxyurea therapy. Nothing is known regarding the pathophysiology and the type of **vascular damage** leading to this syndrome. Here we report a case of a 49-year-old male presenting with gangrene of the toes of both feet 4.5 years after initiation of hydroxyurea therapy for chronic myelogenous leukemia. Blisters on the toes occurred for the first time 9 months prior to hospitalization. Successively, all ten toes showed signs of beginning gangrene with one toe removed surgically 8 months before admission. Presence of diabetes mellitus or peripheral angiopathy was ruled out and platelet counts were within the physiologic range during the last years, excluding thrombocythemia as another rare cause for gangrene in patients with myeloproliferative diseases. Whereas perimalleolar ulcerations of the legs are a more common complication of hydroxyurea, gangrene of the toes as a consequence of hydroxyurea treatment has been described previously only once in the literature. At this point in time cessation of hydroxyurea treatment appears to be the only therapeutic option, thereby avoiding further progress of gangrene in patients with chronic myelogenous leukemia treated with hydroxyurea.

1/9/14 (Item 14 from file: 5)

13932892 BIOSIS NO.: 200200561713
Wavelength-dependent properties of photodynamic therapy using hypericin in vitro and in an animal model.
AUTHOR: Blank Michael; Kostenich Genady(a); Lavie Gad; Kimel Sol; Keisari Yona; Orenstein Arie
AUTHOR ADDRESS: (a)Advanced Technology Center, Sheba Medical Center, Tel Hashomer, 52621**Israel E-Mail: genakos@sheba.health.gov.il
JOURNAL: Photochemistry and Photobiology 76 (3):p335-340 September, 2002
MEDIUM: print
ISSN: 0031-8655
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Wavelength effects in photodynamic therapy (PDT) with hypericin (HY) were examined in a C26 colon carcinoma model both in vitro and in vivo. Irradiation of HY-sensitized cells in vitro with either 550 or 590 nm caused the loss of cell viability in a drug- and light-dose-dependent manner. The calculated ratio of HY-based PDT (HY-PDT) efficiencies at these two wavelengths was found to correlate with the numerical ratio of absorbed photons at each wavelength. In vivo irradiation of C26-derived tumors, 6 h after intraperitoneal administration of HY (5 mg/kg), caused extensive **vascular damage** and tumor necrosis. The depth of tumor necrosis (d) was more pronounced at 590 than at 550 nm and increased when the light dose was raised from 60 to 120 J/cm2. The maximal depths of tumor necrosis (at 120 J/cm2) were 7.5+-1.5 min at 550 nm and 9.9+-0.8 mm at 590 mm. Both values are rather high in view of the limited penetration of green-yellow light into the tissue. Moreover, the depth ratio, d590/d550=1.3 (P<0.001), is smaller than expected considering the 2.2-fold lower HY absorbance and the 1.7-fold lower tissue penetration of radiation at 550 than at 590 nm. This finding indicates that in vivo the depth at which HY-PDT elicits tumor necrosis is not only determined by photophysical considerations (light penetration, number of absorbed photons) but is also influenced significantly by other mechanisms such as vascular effects. Therefore, despite the relatively short-wavelength peaks of absorption, our observations suggest that HY is an effective photodynamic agent that can be useful in the treatment of tumors with depths in the range of 1 cm.

REGISTRY NUMBERS: 548-04-9: HYPERICIN

09/890,989

Your SELECT statement is:
s s(w)methyl(w)L(w)thiocitrulline

Items	File
48	5: Biosis Previews(R)_1969-2002/Nov W3
41	34: SciSearch(R) Cited Ref Sci_1990-2002/Nov W4
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33	73: EMBASE_1974-2002/Nov W2
5	98: General Sci Abs/Full-Text_1984-2002/Oct
22	144: Pascal_1973-2002/Nov W3
1	149: TGG Health&Wellness DB(SM)_1976-2002/Nov W2
37	155: MEDLINE(R)_1966-2002/Nov W3
7	156: ToxFile_1965-2002/Nov W3
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File 5:Biosis Previews(R) 1969-2002/Nov W3
(c) 2002 BIOSIS
***File 5: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 34:SciSearch(R) Cited Ref Sci 1990-2002/Nov W4
(c) 2002 Inst for Sci Info
***File 34: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Nov W3
***File 155: For updating information please see Help News155. Alert** feature enhanced with customized scheduling. See HELP ALERT.

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S3	76	S2 NOT PY=>1999
S4	22	S3 AND (ANGIO? OR VASCUL?)
S5	10	RD (unique items)

5/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11674232 BIOSIS NO.: 199800455963
Calcium-dependent nitric oxide production is involved in arsenite-induced micronuclei.
AUTHOR: Gurr Jia-Ran; Liu Fount; Lynn Shugene; Jan Kun-Yan(a)
AUTHOR ADDRESS: (a)Inst. Zool., Acad. Sinica, Taipei 11529**Taiwan
JOURNAL: Mutation Research 416 (3):p137-148 Aug. 14, 1998
ISSN: 0027-5107
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Arsenic, a human carcinogen is known to induce sister-chromatid exchanges, chromosome aberrations and micronuclei (MN), but its mechanisms remain unknown. Recently, independent studies have suggested that intracellular calcium and reactive oxygen species are involved in arsenite-induced MN, and nitric oxide (NO) is involved in arsenite-induced poly(ADP-ribosylation). The aim of this research is to investigate the involvement of these molecules in arsenite-induced MN. The intracellular oxidant level and calcium level were monitored with a flow cytometer by using dichlorofluorescein diacetate and fluo3-AM, respectively. The NO production was estimated from the nitrite in cell culture medium with a spectrophotometer by using diaminonaphthalene. The results show that a 4-h treatment with arsenite above 5 muM, caused a dose-dependent increase of oxidant, NO, as well as intracellular calcium level. The arsenite-increased intracellular oxidant level was inhibited by NO synthase inhibitors, **S - methyl - L - thiocitrulline** and Nomega-nitro-L-arginine methyl ester and calcium chelators, ethylene glycol-bis (beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid, and

2-((2-bis-(carboxymethyl)-amino-5-methylphenoxy)-methyl)-6-methoxy-8-bis(carboxy-methyl)aminoquinoline, but not by catalase inhibitor, 3-aminotriazole. The arsenite-increased NO could also be suppressed by NO synthase inhibitors and calcium chelator. However, the arsenite-increased intracellular calcium level was inhibited by calcium chelators, but not by NO synthase inhibitors. A 4-h treatment with arsenite above 10 muM, also induced MN dose-dependently. The arsenite-increased MN could be reduced by NO synthase inhibitors, calcium chelators, as well as superoxide dismutase and uric acid. These results suggest the involvement of peroxynitrite in arsenite-induced MN. We surmise that the disturbance of NO production may cause cardio/peripheral **vascular** disorders, and the peroxynitrite-mediated DNA damages may cause genetic instability and, hence, cancers in arsenic-exposed humans.

REGISTRY NUMBERS: 7440-70-2: CALCIUM; 10102-43-9: NITRIC OXIDE; 15502-74-6: ARSENITE; 125978-95-2: NITRIC OXIDE SYNTHASE; 7440-70-2D: CALCIUM; 9054-89-1: SUPEROXIDE DISMUTASE; 69-93-2: URIC ACID

5/9/2 (Item 2 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

11647002 BIOSIS NO.: 199800428733

Comparison between endothelial and neuronal nitric oxide pathways in rat aorta and gastric fundus.

AUTHOR: Guilmard Christine; Auguet Michel; Chabrier Pierre-Etienne(a)
AUTHOR ADDRESS: (a)Inst. Henri Beaufour Res. Lab., 5 Avenue Canada, 91966 Les Ulis Cedex**France

JOURNAL: Nitric Oxide 2 (3):p147-154 1998
ISSN: 1089-8603
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study examines the ability of different nitric oxide synthase (NOS) inhibitors and NO donors to inhibit the endothelium-dependent relaxation of the rat aorta and the NANC relaxation of the rat gastric fundus. NG-Nitro-L-arginine, N-monomethyl-L-arginine, and **S - methyl - L - thiocitrulline** elicit comparable potency in the aorta and in the fundus. However, 1-(2-trifluoromethyl)imidazole (TRIM), unlike 7-nitroindazole, is more potent on the fundus than on the aorta, showing that TRIM elicits a selective functional inhibition of the neural NOS isoform. (1H)-(1,2,4)Oxadiazole(4,3-alpha)quinoxalin-1-one, a selective inhibitor of soluble guanylyl cyclase, inhibits the dilator response in both tissues and the cyclic GMP mimetic, 8-Br-cGMP, is 16 times more potent for inducing relaxation in the gastric fundus than in the aorta. However, methylene blue and LY-83583, two other inhibitors of soluble guanylyl cyclase and superoxide anion-generating agents, are at least 106 times less potent on fundus strips than on aortic rings. The data suggest that once released into the extracellular space, NO is more susceptible to inactivation by superoxide anions in the **vascular** tissue than in the gastric fundus. Thus, the study shows that selective inhibition of NO in a target tissue may be reached not only at the NOS isoform level but also by the manipulation of the NO pathway.

REGISTRY NUMBERS: 10102-43-9: NITRIC OXIDE; 125978-95-2: NITRIC OXIDE SYNTHASE

5/9/3 (Item 3 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

11439696 BIOSIS NO.: 199800221028

Neuronal nitric oxide synthase modulates rat renal microvascular function.

AUTHOR: Ichihara Atsuhiro; Inscho Edward W; Imig John D; Navar L Gabriel
AUTHOR ADDRESS: Dep. Physiol., Tulane Univ. Sch. Med., New Orleans, LA 70112-2699**USA

JOURNAL: American Journal of Physiology 274 (3 PART 2):pF516-F524 March, 1998
ISSN: 0002-9513
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study was performed to determine the influence of neuronal nitric oxide synthase (nNOS) on renal arteriolar tone under conditions of normal, interrupted, and increased volume delivery to the macula densa segment and on the microvascular responses to **angiotensin** II (ANG II). Experiments were performed in vitro on afferent (21.2 +- 0.2 mum) and efferent (18.5 +- 0.2 mum) arterioles of kidneys harvested from male Sprague-Dawley rats, using the blood-perfused juxtamedullary nephron technique. Superfusion with the specific nNOS inhibitor, **S - methyl - L - thiocitrulline** (L-SMTC), decreased afferent and efferent arteriolar diameters, and these decreases in arteriolar diameters were prevented by interruption of distal volume delivery by papillectomy. When 10 mM acetazolamide was added to the blood perfusate to increase volume delivery to the macula densa segment, afferent arteriolar vasoconstrictor responses to L-SMTC were enhanced, but this effect was again completely prevented after papillectomy. In contrast, the arteriolar diameter responses to the nonselective NOS inhibitor, Nomega-nitro-L-arginine (L-NNA) were only attenuated by papillectomy. L-SMTC (10 muM) enhanced the efferent arteriolar vasoconstrictor response to ANG II but did not alter the afferent arteriolar vasoconstrictor responsiveness to ANG II. In contrast, L-NNA (100 muM) enhanced both afferent and efferent arteriolar vasoconstrictor responses to ANG II. These results indicate that the modulating influence of nNOS on afferent arteriolar tone of juxtamedullary nephrons is dependent on distal tubular fluid flow. Furthermore, nNOS exerts a differential modulatory action on the juxtamedullary microvasculature by enhancing efferent, but not afferent, arteriolar responsiveness to ANG II.

5/9/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11305258 BIOSIS NO.: 199800086590
Arsenite stimulates poly (ADP-ribosylation) by generation of nitric oxide.
AUTHOR: Lynn Shugene; Shiung Jaw-Nan; Gurr Jia-Ran; Jan K Y(a)
AUTHOR ADDRESS: (a)Inst. Zool., Academia Sinica, Taipei 11529**Taiwan
JOURNAL: Free Radical Biology & Medicine 24 (3):p442-449 Feb., 1998
ISSN: 0891-5849
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent studies indicate that arsenic may generate reactive oxygen species to exert its toxicity. Because reactive oxygen species are known to induce poly (ADP-ribosylation), which is implicated in DNA repair, signal transduction, and apoptosis, we have investigated the effect of arsenite on poly(ADP-ribosylation). The results showed that arsenite treatment induced poly (ADP-ribosylation), NAD depletion, DNA strand breaks, and micronuclei in CHO-K1 cells. Increase of nitrite level, a stable product of nitric oxide, was also detected in medium of arsenite-treated cultures. **S - methyl - L - thiocitrulline** and Nomega-nitro-L-arginine methyl ester, inhibitors of nitric oxide synthase, could suppress the arsenite-induced NAD depletion, DNA strand breaks, and micronuclei, whereas 3-aminobenzamide, an inhibitor of poly (ADP-ribose) polymerase, could enhance micronucleus production and NAD depletion in arsenite-treated cells. These results suggest that arsenite treatment may generate nitric oxide to damage DNA and which then stimulate poly(ADP-ribosylation). Because arsenite also induced DNA strand breaks and NAD depletion in bovine aortic endothelial cells, and these could also be suppressed by **S - methyl - L - thiocitrulline** , the induction of nitric oxide may be important to the etiology of arsenic-induced **vascular** disorders in humans.

REGISTRY NUMBERS: 15502-74-6: ARSENITE; 10102-43-9: NITRIC OXIDE; 53-84-9: NAD; 7782-44-7: OXYGEN

5/9/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09909665 BIOSIS NO.: 199598364583

Characterization of the effects of two new arginine/citrulline analogues on constitutive and inducible nitric oxide synthases in rat aorta.

AUTHOR: Joly Ghislaine A; Narayanan Krish; Griffith Owen W; Kilbourn Robert G(a)

AUTHOR ADDRESS: (a)Dep. Genitourinary Oncology, Univ. Texas M.D. Anderson Cancer Center, Houston, TX 77030**USA

JOURNAL: British Journal of Pharmacology 115 (3):p491-497 1995

ISSN: 0007-1188

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: 1 New potent inhibitors of nitric oxide synthase (NOS) may be useful in the treatment of septic shock, a disorder characterized by a **vascular** hyporeactivity to catecholamines caused by an overproduction of nitric oxide (NO-). We examined the effects of L-thiocitrulline (L-TC) and **S - methyl - L - thiocitrulline** (LSMTC), novel NOS inhibitors, on the constitutive and inducible NOS in rat aorta and compared those effects with inhibition due to N-G-methyl-L-arginine (L-NMA). 2 Phenylephrine evoked similar concentration-contraction curves in the control rings and in the rings treated with these different NOS inhibitors (10 mu-M), whereas 100 mu-M of L-NMA, L-TC or L-SMTC increased significantly, and to a similar extent, contractions evoked by phenylephrine in aortic rings with endothelium without significantly affecting the maximal responses. 3 Relaxations evoked by acetylcholine, adenosine triphosphate, or calcium ionophore were significantly inhibited in a dose-dependent manner by L-NMA, L-SMTC, or L-TC (10-100 mu-M). The potencies of these inhibitors in reducing the relaxations of these vasodilators were not significantly different. 4 In endotoxin-treated preparations with endothelium, the three L-arginine analogues (10 mu-M) significantly potentiated contractile responses to phenylephrine (pEC-50: 6.73 +- 0.12 and 7.3 +- 0.12, 7.34 +- 0.13, or 7.22 +- 0.14; in the absence and the presence Of L-NMA, L-TC, or L-SMTC respectively) and increased maximal contractions from 1.53 +- 0.15 g to 1.95 +- 0.13 g, 2.08 +- 0.12 g, and 2.03 +- 0.13 g with L-NMA, L-TC, and L-SMTC respectively. A higher concentration of these NOS inhibitors 100 mu-M) further increased contractions evoked by this alpha-1-agonist without further enhancing the maximal contractions; however, contractions evoked by 10 nM phenylephrine were significantly greater in the presence of L-SMTC or L-TC than in the presence Of L-NMA (100 mu-M) (L-NMA: 0.4 +- 0.11 g; L-TC: 0.78 +- 0.14 g and L-SMTC: 0.82 +- 0.17 g). The effects of these inhibitors on NO- synthesis induced by endotoxin were significantly reversed by addition of L-arginine (1 mM) but not by L-Citrulline (1 mM). In LPS-treated rings with endothelium, all three NOS inhibitors (100 Mm) shifted the concentration-contraction curves evoked by phenylephrine significantly to the left (pEC-50: 7.19 +- 0.03 and 7.79 +- 0.08, 8.01 +- 0.07, or 8.02 +- 0.07, in the absence and the presence of L-NMA, L-TC, or L-SMTC, respectively) and increased significantly maximal contractions from 2.05 +- 0.05 g to 2.38 +- 0.14 g, 2.5 +- 0.12 g, and 2.4 +- 0.21 g with L-NMA, L-TC, and L-SMTC, respectively. L-TC and L-SMTC were significantly more potent than L-NMA in potentiating contractions evoked by 10 nM and 30 nM phenylephrine. 5 L-TC and L-SMTC produced dose-dependent increases in tone in LPS-treated aortic rings with and without endothelium. In LPS-treated rings with endothelium, L-NMA induced contractions but in preparations without endothelium low concentrations of L-NMA induced small contractions while high concentrations of this inhibitor evoked relaxations. In both preparations L-TC and L-SMTC were significantly more potent than L-NMA in increasing **vascular** tone. 6 These results suggest that L-SMTC, L-TC and L-NMA were equipotent on basal and agonist-stimulated NO- synthesis produced by the constitutive isoform of NOS, whereas the two new L-arginine analogues were more potent than L-NMA in inhibiting the production of NO- induced by endotoxin in rat aorta.

REGISTRY NUMBERS: 74-79-3: ARGININE; 125978-95-2D: NITRIC OXIDE SYNTHASES; 2149-70-4: N-NITRO-L-ARGININE

5/9/6 (Item 6 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

09554435 BIOSIS NO.: 199598009353
Potent and selective inhibition of human nitric oxide synthases: Selective inhibition of neuronal nitric oxide synthase by S - methyl - L - thiocitrulline **and S-ethyl-L-thiocitrulline.**
AUTHOR: Furfine Eric S(a); Harmon Marilyn F; Paith Jerilin E; Knowles Richard G; Salter Mark; Kiff Rachel J; Duffy Claire; Hazelwood Robert; Oplinger Jeffrey A; Garvey Edward P
AUTHOR ADDRESS: (a)Div. Experimental Therapy, Wellcome Res. Lab., Research Triangle Park, NC 27709**USA
JOURNAL: Journal of Biological Chemistry 269 (43):p26677-26683 1994
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Potent and selective inhibition of neuronal nitric oxide synthase (nNOS) compared to endothelial NOS (eNOS) and inducible NOS (iNOS) may be useful to treat cerebral ischemia (stroke) and other neurodegenerative diseases. **S - Methyl - L - thiocitrulline** (Me-TC) and S-ethyl-L-thiocitrulline (Et-TC) inhibited the oxidation of L-arginine and the L-arginine-independent oxidation of NADPH by nNOS from human brain. Me-TC and Et-TC were slow, tight binding inhibitors of nNOS with second-order association rate constants (k-on) of 2.6 times 10-5 m-1 s-1 and 1.3 times 10-5 m-1 s-1, respectively. The respective dissociation rate constants (k-off) were 3 times 10-4 s-1 and 0.7 times 10-4 s-1. Thus, the K-d values calculated from k-off/k-on were 1.2 and 0.5 nM, respectively. L-Arginine was a competitive inhibitor of Me-TC and Et-TC binding with competition constant (K-m) values of 2.2 and 2.7 mu-M, respectively. The K-m of nNOS for L-arginine was 1.6 mu-M. The active site concentration of nNOS was estimated by titration with Et-TC. Based on this active site concentration, a k-cat of 0.4 s-1 for the oxidation of L-arginine, was calculated. Me-TC and Et-TC were less potent inhibitors of human iNOS (K-i values of 34 and 17 nM, respectively) and human eNOS (K-i values of 11 and 24 nM). Thus, Me-TC and Et-TC were 10- and 50-fold, respectively, more potent inhibitors of nNOS than eNOS. Furthermore, Me-TC was also 17-fold selective for rat nNOS in neuronal tissue compared to rat eNOS in **vascular** endothelium, suggesting that Me-TC may be selective for nNOS in vivo and therefore, may be therapeutically useful to treat neurodegenerative diseases.

REGISTRY NUMBERS: 125978-95-2: NITRIC OXIDE SYNTHASES; 125978-95-2: NITRIC OXIDE SYNTHASE; 158875-72-0: S-ETHYL-L-THIOCITRULLINE

5/9/7 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06151193 Genuine Article#: XY698 Number of References: 39
Title: Influence of different classes of NO synthase inhibitors in the pig gastric fundus
Author(s): Dick JMC; Lefebvre RA (REPRINT)
Corporate Source: HEYMANS INST PHARMACOL,DE PINTELAAN 185/B-9000 GHENT//BELGIUM/ (REPRINT); HEYMANS INST PHARMACOL,/B-9000 GHENT//BELGIUM/
Journal: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, 1997, V356, N4 (OCT), P488-494
ISSN: 0028-1298 Publication date: 19971000
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Geographic Location: BELGIUM
Subfile: CC LIFE--Current Contents, Life Sciences
Journal Subject Category: PHARMACOLOGY & PHARMACY
Abstract: The inhibitory potency of different classes of nitric oxide synthase (NOS) inhibitors (amino acid-based substances, guanidines, isothioureas, imidazoles and indazoles) versus peripheral neuronal NOS in the pig gastric fundus was investigated by studying their influence on electrically induced relaxations in non-adrenergic noncholinergic conditions. Circular muscle strips were mounted for isotonic

registration in the presence of atropine and guanethidine, and tone was raised with 5-hydroxytryptamine. Electrical field stimulation (40 V, 0.1 ms, 4 Hz, 10 s) induced short-lasting relaxations. The inhibitory effect of 1-phenylimidazole could not be evaluated because it nearly abolished the 5-hydroxytryptamine-induced tone of the tissues. 7-Nitroindazole, imidazole, 2-iminobiotin and aminoguanidine did not inhibit the electrically induced relaxations, while the other 9 substances tested were able to do so. The influence of the incubation period was tested by studying the inhibitory effect after incubation for 10 up to 60 min. For N-G-nitro-L-arginine methyl ester (L-NAME), N-G-nitro-L-arginine (L-NNA), L-N-5-(1-iminoethyl)-ornithine (L-NIO), L-N-6-(1-iminoethyl)-lysine (L-NIL), **S - methyl - L - thiocitrulline** and S-isopropyl isothiourea there was a moderate increase in the inhibitory effect up to 30 min of incubation so that they were incubated for 30 min to study their inhibitory potency. For L-thiocitrulline, S-methyl isothiourea and S-ethyl isothiourea, an incubation period of 60 min was used. The 9 substances concentration-dependently inhibited the electrically induced relaxations with a maximal inhibitory effect of approximately 80% except for S-methyl isothiourea (E-max of 53%). The over all order of potency was: S-isopropyl isothiourea > S-ethyl isothiourea greater than or equal to **S - methyl - L - thiocitrulline** greater than or equal to L-NNA > L-NIO > L-NAME > S-methyl isothiourea > L-thiocitrulline > L-NIL. While the potency for S-isopropyl isothiourea (EC50: 3.1x10(-5) M, n = 6) to S-methyl isothiourea (EC50: 11.5x10(-5) M, n = 5) was in the same range, the potency of L-thiocitrulline and L-NIL was clearly lower. This study showed several compounds to be potent inhibitors of peripheral neuronal NOS in the pig gastric fundus while some compounds, that were reported to inhibit brain neuronal NOS were not effective. The EC,, values found for the effective substrates in this functional study may be a guideline for the concentrations required to evaluate the role of NO in NANC neurotransmission in gastrointestinal smooth muscle preparations.

5/9/8 (Item 2 from file: 34)

03983907 Genuine Article#: QX865 Number of References: 51

Title: S-ALKYL-L-THIOCITRULLINES - POTENT STEREOSELECTIVE INHIBITORS OF NITRIC-OXIDE SYNTHASE WITH STRONG PRESSOR ACTIVITY IN-VIVO

Author(s): NARAYANAN K; SPACK L; MCMILLAN K; KILBOURN RG; HAYWARD MA; MASTERS BSS; GRIFFITH OW
Corporate Source: MED COLL WISCONSIN,DEPT BIOCHEM,8701 WATERTOWN PLANK RD/MILWAUKEE//WI/53226; MED COLL WISCONSIN,DEPT BIOCHEM/MILWAUKEE//WI/53226; MED COLL WISCONSIN,DEPT PEDIAT/MILWAUKEE//WI/53226; UNIV TEXAS,HLTH SCI CTR,DEPT BIOCHEM/SAN ANTONIO//TX/78284; UNIV TEXAS,MD ANDERSON CANC CTR,DEPT MED ONCOL/HOUSTON//TX/77030

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1995, V270, N19 (MAY 12), P 11103-11110
ISSN: 0021-9258
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY

Abstract: Nitric oxide synthase catalyzes the oxidation of a guanidino nitrogen of L-arginine to nitric oxide with concomitant formation of citrulline, Enzyme activity is inhibited by a variety of N-omega-monosubstituted L-arginine analogs including N-omega-alkyl-, N-omega-amino-, and N-omega-nitro-L-arginine derivatives, We report here that both constitutive and inducible isoforms of nitric oxide synthase are strongly inhibited by S-alkyl-L-thiocitrullines (N-delta-(S-alkyl)isothioureido-L ornithines) with n-alkyl groups of one to three carbons, These compounds represent a novel class of inhibitors and are the most potent nitric oxide synthase inhibiting amino acids described to date. Inhibition is reversible, stereoselective, and competitive with L-arginine, Spectral studies show no direct interaction of inhibitor sulfur with heme iron, a result in contrast to that seen previously with the parent compound,

L-thiocitrulline. The S-alkyl-L-thiocitrullines have strong presser activity in normotensive control rats; **S - methyl - L - thiocitrulline** reverses hypotension in a rat model of septic peritonitis and in dogs administered endotoxin, These latter findings suggest that the inhibitors may have therapeutic utility in treating hypotension due to the overproduction of nitric oxide.

5/9/9 (Item 3 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03094643 Genuine Article#: NE357 Number of References: 26

Title: SYNTHESIS OF L-THIOCITRULLINE, L-HOMOTHIOCITRULLINE, AND S - METHYL - L - THIOCITRULLINE **- A NEW CLASS OF POTENT NITRIC-OXIDE SYNTHASE INHIBITORS**

Author(s): NARAYANAN K; GRIFFITH OW
Corporate Source: MED COLL WISCONSIN,DEPT BIOCHEM,8701 WATERTOWN PLANK RD/MILWAUKEE//WI/53226; MED COLL WISCONSIN,DEPT BIOCHEM/MILWAUKEE//WI/53226

Journal: JOURNAL OF MEDICINAL CHEMISTRY, 1994, V37, N7 (APR 1), P885-887
ISSN: 0022-2623
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: CHEMISTRY, CLINICAL & MEDICINAL

Abstract: Nitric oxide synthase catalyzes the NADPH- and O-2-dependent conversion of L-arginine to L-citrulline and nitric oxide. L-Thiocitrulline, L-homothiocitrulline, and **S - methyl - L - thiocitrulline** , novel citrulline analogs, have been synthesized and are shown to be potent inhibitors of both the constitutive brain and the inducible smooth muscle isoforms of nitric oxide synthase. Although many N-omega-monosubstituted arginine derivatives inhibit nitric oxide synthase, inhibitory citrulline derivatives have not previously been reported. **S - Methyl - L - thiocitrulline** is significantly more potent than N-omega-methyl-L-arginine, the prototypic nitric oxide synthase inhibitor.

5/9/10 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09991088 98431938 PMID: 9755132

Cyclooxygenase-2 participates in tubular flow-dependent afferent arteriolar tone: interaction with neuronal NOS.

Ichihara A; Imig J D; Inscho E W; Navar L G
Department of Physiology, Tulane University School of Medicine, New Orleans, Louisiana 70112-2699, USA.

American journal of physiology (UNITED STATES) Oct 1998, 275 (4 Pt 2) pF605-12, ISSN 0002-9513 Journal Code: 0370511
Contract/Grant No.: HL-18426; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS

To delineate the microvascular role of cyclooxygenase-2 (Cox-2) in modulating tubuloglomerular feedback (TGF) signals and to determine its relationship to neuronal nitric oxide synthase (nNOS), afferent (AA) and efferent (EA) arteriolar diameters of rat kidneys were assessed using the blood-perfused juxtamedullary nephron technique. The Cox-2 inhibitor NS-398 (10 microM) did not alter AA diameters in untreated kidneys but significantly constricted AAs by 17.0 +/- 2.2% in kidneys treated with 10 mM acetazolamide, which enhances TGF-mediated AA constriction by increasing distal volume delivery. The NS-398-induced AA constriction was prevented after interruption of distal delivery by transection of the loops of Henle. The effect was selective for AAs since NS-398 did not influence EAs of untreated or acetazolamide-treated kidneys. Pretreatment with the nNOS inhibitor **S - methyl - L - thiocitrulline** (10 microM) prevented the NS-398-induced AA constriction observed during acetazolamide treatment. Although we previously demonstrated that acetazolamide treatment enhanced AA constrictor response to **S - methyl - L - thiocitrulline** , the enhancement by acetazolamide was inhibited by pretreatment with 10 microM

NS-398 (16.4 +/- 1.9 and 15. 0 +/- 0.5% with and without acetazolamide, respectively, P > 0.05). These results indicate that, during increased activation of TGF-dependent vasoconstrictor signals, Cox-2 generates vasodilatory metabolites in response to increased nNOS activity and thus participates in the counteracting modulation of TGF-mediated AA constriction.

Your SELECT statement is:
s n(w)acetylcolchinol

Items	File
11	5: Biosis Previews(R)_1969-2002/Nov W3
6	34: SciSearch(R) Cited Ref Sci_1990-2002/Nov W4
2	35: Dissertation Abs Online_1861-2002/Oct
10	73: EMBASE_1974-2002/Nov W3
6	144: Pascal_1973-2002/Nov W3
4	155: MEDLINE(R)_1966-2002/Nov W3
1	172: EMBASE Alert_2002/Nov W3
5	399: CA SEARCH(R)_1967-2002/UD=13721
3	434: SciSearch(R) Cited Ref Sci_1974-1989/Dec

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File 155:MEDLINE(R) 1966-2002/Nov W3
***File 155: For updating information please see Help News155. Alert** feature enhanced with customized scheduling. See HELP ALERT.

Set	Items	Description
S1	25	N(W)ACETYLCOLCHINOL
S2	20	RD (unique items)
S3	15	S2 NOT PY=>2000

3/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12746375 BIOSIS NO.: 200000499998
The novel vascular targeting agent ZD6126 causes rapid morphology changes leading to endothelial cell detachment at non-cytotoxic concentrations.
AUTHOR: Blakey D C(a); Douglas S(a); Revill M(a); Ashton S A(a)
AUTHOR ADDRESS: (a)Cancer and Infection Bioscience Dept, AstraZeneca, Alderley Park, Macclesfield, Cheshire, SK10 4TG**UK
JOURNAL: Clinical & Experimental Metastasis 17 (9):p776 1999
MEDIUM: print
CONFERENCE/MEETING: VIII International Congress of the Metastasis Research Society London, UK September 24-27, 2000
ISSN: 0262-0898
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
DESCRIPTORS:
MAJOR CONCEPTS: Pharmacology; Cardiovascular System (Transport and Circulation); Tumor Biology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: HUVEC cell line (Hominidae)--drug-induced cell detachment, drug-induced cell shape changes, human umbilical vein endothelial cell line
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates
DISEASES: cancer--drug-induced angiogenesis inhibition, neoplastic disease
CHEMICALS & BIOCHEMICALS: **N - acetylcolchinol** prodrug {ZD-6126}--antineoplastic-drug, tubulin binding agent, tumor antiangiogenic activity, vascular targeting agent
MISCELLANEOUS TERMS: Meeting Abstract; Meeting Poster
ALTERNATE INDEXING: Neoplasms (MeSH)